phine was administered subcutaneously in place of the 30-mg dose. Four to 6 weeks after termination of lithium administration, a 7.5-mg dose of morphine was again given to each subject. This is a near-threshold dose for detection of subjective effects in this population.

The subjective, euphoric, and pupillary effects of each dose of morphine and placebo were measured at each time with a standard procedure (*7, 10, 11*). At 7 and 7:30 a.m., pupillary diameter was determined photographically. At 8 a.m., morphine or placebo was injected subcutaneously under double-blind conditions. Change in pupillary diameter was determined photographically 0.5, 1, 2, 3, 4, and 5 hours later; subjects and observers answered questionnaires at the same six times. From these questionnaires, scores were calculated on scales measuring the subjective, euphoric, and behavioral effects of morphine. From subject responses, these were scores on the opiate symptom and subject liking scales (*10, 11*) and on a subset of items from the MBG scale (*7*). Opiate sign and observers' liking scale scores were obtained from observers' responses (*9, 11*). The six scores after drug injection for change in pupillary diameter and for each scale were summed (total 5-hour scores) to serve as the measure of drug response.

Comparison of the responses to morphine during lithium administration to those before and after lithium administration indicates that lithium did not block the euphoric, subjective, or miotic effects of morphine (Table 2). In fact, morphine (15 mg) was significantly more euphoric during lithium administration, as measured by subjects' liking scores. The slight decrease in MBG scores and increase in observers' liking and opiate sign scale scores with placebo response during lithium administration (Table 2) is attributed to the effects of lithium itself.

These studies indicate that (i) lithium itself is antieuphoric in nonmanic subjects, and its profile of subjective effects most closely resembles that for a small dose of chlorpromazine; and (ii) lithium does not block morphine-induced euphoria. Further, these observations argue against a common mechanism for euphoria.

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5 April 1976; revised 6 July 1976

Basal Ganglia Cooling Disables Learned Arm Movements of Monkeys in the Absence of Visual Guidance

Abstract. *Unilateral local cooling in the region of the globus pallidus of Cebus monkeys produced a severe breakdown in the performance of learned flexion-extension elbow movements when animals had no visual information about arm position but not when such information was displayed to them. This result indicates that visual information enables an animal to compensate to a large degree for the motor disorder produced by globus pallidus dysfunction, and it may explain why some previous workers have failed to see motor impairments in monkeys with lesions in the globus pallidus who were observed in their cages.*

The globus pallidus (GP) (a major efferent nucleus of the basal ganglia) has recently been implicated in motor control. For example, a correlation has been found between firing of single units in the GP and movements of the contralateral limbs (*1*). This finding is in keeping with anatomical studies (*2*) that have emphasized the functional significance of the input to basal ganglia from all areas of cerebral cortex and the output from the GP to thalamic nuclei, which project to cerebral motor cortex. However, the exact function of the GP in motor control is still not clear. In the early ablation studies in animals, lesions of the GP were found to produce no obvious motor defects (*3*). It was only when large bilateral lesions were made in the GP that monkeys were found to adopt a flexion posture of the limbs and to lose placing and righting reactions (*4*). From his studies on human patients with diseases that produced lesions in the basal ganglia, Martin (*5*) concluded that bilateral lesions of the GP produced loss of postural reflexes. In one test for motor defects, patients were asked to reach out with their arm at shoulder height and touch alternately the tips of the examiner's two forefingers, which were held about a foot apart. With their eyes open the patients continued to perform well for several minutes, ". . . but if after the first movements he closes his eyes, the hand almost immediately falls away and the movement peters out" (*5*, p. 13).

In an attempt to produce an animal model of such diseases we have implanted cooling sheaths in the GP in four Cebus monkeys (*6*). Some preliminary results have been reported as abstracts (*7*). Cooling through cryoprobes inserted into these sheaths produced a temporary functional lesion, which was restricted to the brain region surrounding the sheath (Fig. 1). Motor performance of these monkeys was tested in a behavioral situation similar to that of the patients. Monkeys were trained to move a handle in a horizontal arc of about 60° between two target positions by making alternate flexion and extension movements at the elbow. Animals were rewarded with a drop of fruit juice for making three alternate movements during which the handle had to be held in each of the 20° targets for 0.2 second. The animals' view of their limbs was blocked by an opaque plate. At the start of each experimental session, flexion and extension targets were indicated by lights that lit when the handle was in target, thus providing the animals with proprioceptive cues for the position of the targets. After about 10 minutes of practice, the lights were removed and animals continued the alternating movements without any visual cues as to target position. The first monkey tested (M29L) never learned the significance of the visual cues and was rewarded for simply moving the handle from side to side and passing through the targets.

Cooling the right GP in these four monkeys impaired the performance of this simple arm movement task. The monkeys normally made smoothly executed

rhythmic movements (Fig. 1). During cooling this pattern disintegrated and the movements became jerky and smaller in amplitude (especially for extensions) and were made at more irregular intervals. Simultaneously the elbow tended to be held in a flexed posture. The biceps muscle can be imagined as being a spring that stiffens during cooling, decreasing the amplitude of extension movements and increasing the tendency toward a flexion posture (*8*). During GP cooling, movements became inaccurate, and the animals often became "frustrated" at their inability to gain juice reward and took their hands from the handle. On returning the hand to the handle they made a few alternating movements and then the movement pattern broke down again.

This effect was observed in M28L and M29L after cooling to 10°C for 1 minute (all temperatures were read from a thermocouple attached to the sheath 4 mm from its end) and in the other two monkeys after cooling to 10°C for several minutes. The motor impairment was also apparent in M29L after some minutes of cooling to 18°C, a temperature at which fibers passing through (for example, nigrostriatal fibers) were unlikely to have been affected (*9*). Under conditions of severe cooling to below 5°C for several minutes, M28L and M29L made extension movements of only a few degrees of arc and progressively adopted a flexion posture at the elbow and the wrist with extension of the fingers. During severe cooling, the other two monkeys continued to make smaller jerky movements and showed a tendency toward this flexion posture, which resembles that described as a result of carbon disulfide poisoning in man and monkeys, in which bilateral damage was found in the GP (*10*).

Analysis of electromyographic (EMG) recordings of biceps and triceps muscles in all monkeys revealed differences between the normal and cooled conditions. Normally, small EMG bursts alternated in the biceps and the triceps during flexion and extension movements. However, during cooling, an overall increase in EMG activity was usually observed in both muscles, together with periods of cocontraction (*8*). Within 1 to 2 minutes after the end of cooling, normal alternating arm movements and EMG pattern returned again.

Although an attempt was made to select stereotaxic coordinates for sheath implantation so that cooling was focused in the GP, some spread of cooling may have occurred to adjacent neural structures. To investigate the possible involvement of the overlying cerebral cortex and putamen, control experiments were performed in which the cooling probe was withdrawn 5 to 6 mm within the implanted sheath, thereby focusing cooling in the putamen. In this situation, with the sheath thermocouple in the GP at 30°C, no impairment of movement was observed in any of the monkeys. Pushing the probe in once again returned the GP reference temperature to 10°C and movements were again impaired. Although this evidence points to a dysfunction of the GP in producing the motor disorder, cooling was not restricted enough to allow the external or internal segment of the GP to be distinguished or some contribution from cooling the overlying putamen to be ruled out. Involvement of the adjacent internal capsule was excluded by implanting in M29L a further sheath in this structure almost parallel to the one in the GP (Fig. 1). As predicted from previously published isotherms for this cooling system (*11*), cooling the GP sheath to 10°C resulted in a temperature of 33°C measured 5 mm away in the adjacent internal capsule, in which conduction should not have been blocked (*9*). A further control was performed by cooling the internal capsule sheath to 10°C, which resulted in no detectable change in motor performance (presumably corticospinal fibers to arm motoneurons are not affected by this temperature or are not found at this level in the internal capsule).

Evidence from previous animal experiments indicated that motor impairments are more severe, or in fact detectable, only if lesions are made in both the ipsilateral and the contralateral GP (*3*, *4*). This was not confirmed in the present study: cooling the ipsilateral (left) GP to 5°C through another sheath (implanted in a later operation in M29L) produced no effect on motor performance of the left arm and no contributing effect on movement impairment due to contralateral (right) GP cooling.

As had been observed with patients (*5*), visual information enabled the monkeys to compensate in large measure for the motor deficit produced by GP dysfunction. For example, even during severe cooling to below 5°C for many minutes, all monkeys were able, under visual control, to reach out and grasp small pieces of apple accurately with the contralateral arm. This early observation led us to retrain two monkeys to move a

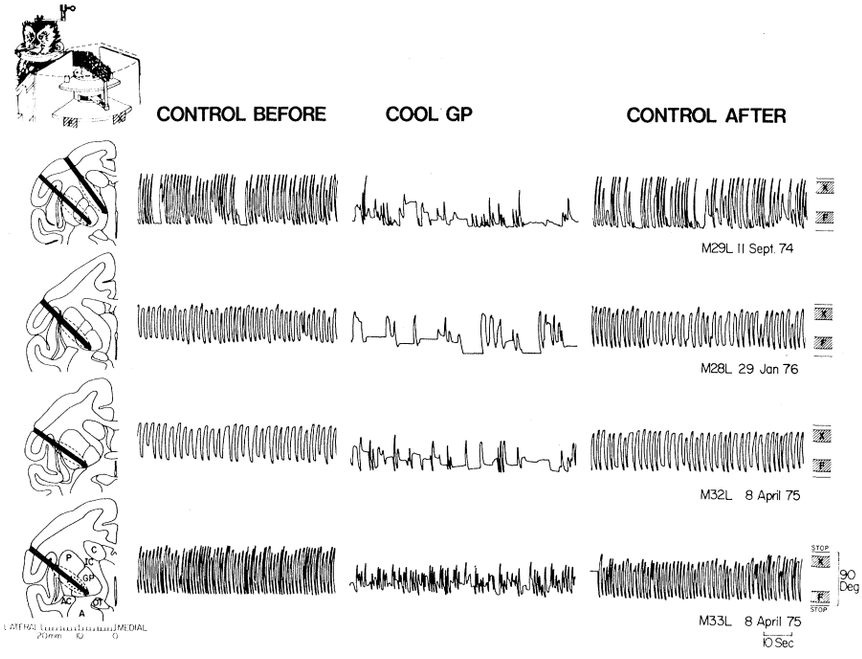

Fig. 1. Impairment during GP cooling (7° to 10°C sheath reference temperature) of self-paced nonballistic elbow movements that were performed without visual guidance. Upper left: drawing of experimental situation with monkey's arm on handle. Dashed line represents opaque plate that blocked the animal's view of its arm. Records show handle position as four monkeys made alternating movements between mechanically undetectable flexion (*F*) and extension (*X*) targets. Impaired movements were seen within minutes after the start of cooling, and normal movements returned again within minutes after cooling was stopped. Left: drawings of frontal sections showing the position of the implanted sheaths for each of the animals whose arm movements are shown to the right. Dashed line shows the estimated 18°C isotherms when sheath thermocouple reads 10°C. To show that cooling is more intense toward the end of the sheath, the 16.5°C isotherm has been drawn as filled circles in the lower left section. Abbreviations: *GP*, globus pallidus; *P*, putamen; *C*, caudate; *IC*, internal capsule; *AC*, anterior commissure; *OT*, optic tract; *A*, amygdala.

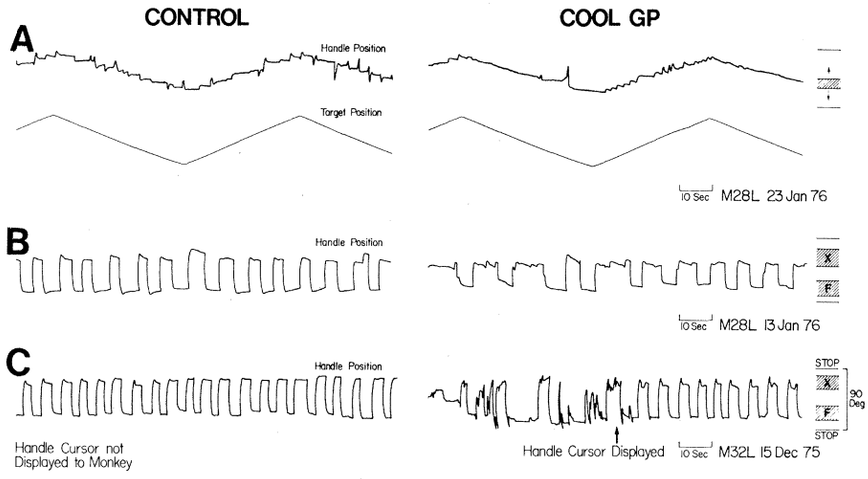

Fig. 2. Successful performance of visually guided elbow movements during GP cooling. Monkeys were rewarded for keeping a handle cursor bar superimposed on a wider target bar, both displayed on an oscilloscope in front of the monkey, as the target bar moved slowly between flexion (*F*) and extension (*X*) positions or jumped in steps between the two positions. (A) Slow pursuit tracking (target and handle cursor displayed): During GP cooling, M28L still performed successfully although movement strategy seemed to be different, for example, drifting when following target toward flexion. (B) Step tracking (target and handle cursor displayed): M28L performed step movements successfully during cooling although some impairment was evident. (C) Step tracking (target displayed): M32L was trained to follow the target either with or without the handle cursor displayed. During cooling, movements disintegrated when handle cursor was not displayed but were reestablished when cursor was displayed (from arrow).

handle in a task in which both target and handle position (handle cursor) were displayed on an oscilloscope facing the monkey. In this task the monkey was rewarded for superimposing the handle cursor on the target bar as it moved slowly between flexion and extension positions [pursuit tracking (Fig. 2A)] or jumped rapidly in steps between the two positions [step tracking (Fig. 2B)]. Although cooling of the GP in this situation produced changes in motor performance in M28L [for example, following the target toward flexion by drifting (Fig. 2A) and making smaller amplitude movements (Fig. 2B)], the animal was still able to perform the visually guided tasks successfully. This is further illustrated in another monkey that had been trained to follow the jumping target with or without having the handle cursor displayed (Fig. 2C). During GP cooling the step movements broke down without the handle cursor present but were performed successfully again when the handle cursor was displayed. Thus all tasks were successfully performed despite GP cooling when the monkeys were given visual information about handle position. Even with visual guidance some impairment of motor performance remained during GP cooling, for example, movements of smaller amplitude and a tendency toward a flexion posture. However, visual information did enable the animals to improve their overall performance. These results may explain why many workers have failed to find motor deficits after making unilateral GP lesions; vision probably enables an animal to compensate to some degree for the motor deficit produced by GP dysfunction.

A recent theory (*12*), which has received some experimental support (*13*), proposes that one function of the basal ganglia is to generate slow voluntary smooth movements. The present experiments were not designed to test this theory and do not provide definitive evidence. However, our results imply that any theory of basal ganglia function must allow for the fact that vision can prevent the disintegration of movement during GP dysfunction. This fact suggests that either (i) visual information allowed the improved function of basal ganglia regions unaffected by cooling, or (ii) there are pathways other than those through basal ganglia by which the brain can control visually guided movements (*14*).

The impaired ability to make alternating movements during contralateral GP cooling in the absence of vision is similar to the situation described by Martin in human patients (*5*). Martin attributed the cause of the defect partly to the loss of postural fixation. This was probably not the only cause of the impairment in our monkeys, as their elbows rested on a pivot. In both humans and monkeys, the motor impairment was most obvious in a task in which feedback about the movement was mainly proprioceptive (that is, from the limb). Thus, another possible explanation of these results could be that the GP normally processes proprioceptive feedback from the limb, although there is scant anatomical or physiological support for this suggestion. It seems that any such proprioceptive information is not used for sensory awareness of limb position, for Martin observed that the patients with basal ganglia lesions retained the sense of limb position. Thus, Martin concluded that the defect produced by GP dysfunction "would seem to be due to disorder of a more complex function which is dependent on proprioception" (*5*, p. 13). However, whether the defect is due to a disorder in processing proprioceptive information, to a disorder in the central programming of movement, or to a release of other neural structures from GP influence will have to await further experimentation. Whatever its exact function, in the absence of vision, the GP must function properly in order for contralateral limb movements to be accurately executed.

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15. This work was supported by the Medical Research Council of Canada grant MT-4465 and U.S. Public Health Service grant NS-10311. This study was performed in part while J.H. held a Muscular Dystrophy Association of Canada postdoctoral fellowship. J.M.-L. was a Fellow of the Deutsche Forschungs Gemeinschaft.
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15 September 1976